

REMARKS

Claims 1-8, 14, 15, 19, 32, 33, 36-52 and 55-59 are pending in the present application. By virtue of this response, claims 56 and 57 have been cancelled and claim 1 has been amended. Support for the amendment of claim 1 is found in the specification, such as in original claim 12. Accordingly, claims 1-8, 14, 15, 32, 33, 36-39, 46-52, and 55 are currently under consideration.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Claims Rejection – 35 U.S.C. § 112, first paragraph

Claims 56-57 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant respectfully traverse this rejection. However, in the interest of expediting prosecution and without acquiescence to the rejection, claims 56 and 57 have been cancelled. Thus, this rejection is moot. Applicant respectfully requests that the rejection be withdrawn.

Claims Rejection – 35 U.S.C. § 103(a)

Claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55-57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Siegall et al. (U.S. Patent No. 6,843,989) (892;of record) in view of Li et al. (U.S. Patent No. 6,495,129), Hanna et al. (US 2001/0018041 A1) and Grillo-Lopez (U.S. Patent No. 6,455,043) (892; of record), Benoit et al. (Immunopharmacology 35: 129-139, 1996) (1449; #59).

Applicant respectfully traverses and reiterates arguments made in the previous responses.

The Examiner states that applicant's arguments are against the references individually and one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. Applicant respectfully disagrees with the Examiner. Applicant respectfully submits that after characterizing the disclosure of each reference, Applicant argued that in view of the teachings of all the references cited by the Examiner, one skilled in the art would not be motivated to administer an anti-CD20 antibody with an anti-CD40 antibody that binds and stimulates CD40, enhances interaction between CD40 and CD40L and arrests the growth of or causes deletion of cells expressing CD40 for treating a neoplastic disease or disorder as claimed. Therefore, Applicant's arguments made in the previous response were based on the teachings in the combination of the references.

Applicant respectfully notes that the references cited by the Examiner in combination do not provide the motivation for one skilled in the art to select antibody S2C6 or an antibody with similar activity (*i.e.*, an antibody which enhances the binding between CD40L and CD40 and stimulates CD40) in combination with an anti-CD20 antibody for the treatment of neoplastic diseases. As demonstrated in Siegall et al., there are different types of anti-CD40 antibodies. For example, some anti-CD40 antibodies inhibit the binding between CD40L and CD40, and other anti-CD40 antibodies enhance the binding between CD40L and CD40 and stimulate CD40. One skilled in the art would not expect that different types of anti-CD40 antibodies have the same effect on cancer cells.

Although general combination treatment with two or more different anti-cancer drugs were known, it was not predictable whether an anti-CD20 antibody and an anti-CD40 antibody combination treatment could achieve at least an additive effect for treating a cancer. As indicated in the Declaration by Dr. Timothy S. Lewis ("Declaration") submitted with this response, combination therapy with an anti-CD20 antibody and an anti-CD40 antibody might achieve an antagonistic effect, no significant improvement, an additive effect, or a synergistic effect, as compared to the corresponding monotherapy, when the optimized of each single agent treatment was used. Further, data in Hanna et al. showed that CD40L-CD40 signaling prevented apoptosis of B-lymphoma cells by anti-CD20 antibody Rituxan®. See Example 3, Table 1. The data in this Example indicated that

activation of the CD40L-CD40 pathway by soluble CD40L (sCD40L) generated resistance of RITUXAN® induced apoptosis in DHL-4 lymphoma cells. Thus, combination treatment with soluble CD40L and RITUXAN® may not provide even additive effects as compared to treatment with each molecule alone. In view of the data, one skilled in the art would not be motivated to select an anti-CD40 antibody (such as antibody S2C6) that enhances the interaction between CD40L and CD40 and stimulates CD40 in combination with an anti-CD20 antibody for treating a neoplastic disease or disorder, and would not reasonably expect that this combination would have at least additive effects for treating a neoplastic disease characterized by cells expressing CD40.

Although data in Benoit et al. may suggest that an anti-CD20 antibody may be combined with an anti-CD40 antibody for treating neoplastic diseases, the data presented in this reference is an *in vitro* assay, and only G28-5 antibody was tested. The Examiner has not provided evidence indicating that the *in vitro* study disclosed in Benoit et al. is predictive for beneficial therapy in animals or humans. As shown in Siegall et al., G28-5 either did not enhance or inhibited the interaction between CD40 and CD40L. This suggests that G28-5 may have a different effect on cancer cells as compared to antibodies that enhance the interaction between CD40 and CD40L and stimulate CD40. Even if the *in vitro* data presented in Benoit et al. would suggest to one skilled in the art that the combination of an anti-CD20 antibody and an anti-CD40 antibody could have additive effect in cancer treatment in animals or humans as the effect shown *in vitro*, the data in this reference does not provide the motivation for one skilled in the art to select another anti-CD40 antibody that has a different effect on CD40, *i.e.*, enhancing the interaction between CD40 and CD40L, for the combination treatment.

Siegall et al. discloses that S2C6 antibody can be used for treating a neoplastic disease or disorder. Grill-Lopez discloses treating neoplastic diseases or disorders with anti-CD20 antibodies. However, neither Siegall et al. nor Grill-Lopez teaches or provides the motivation for a combination therapy with an anti-CD20 antibody and an anti-CD40 antibody having the characteristics of antibody S2C6. As discussed in the previous response, Li et al. does not teach or suggest use of an anti-CD20 antibody in combination with an anti-CD40 antibody for treating a neoplastic disorder.

Taken together, one skilled in the art would not have been motivated to use the combination therapy of an anti-CD40 antibody that enhances the interaction between CD40L and stimulates CD40 and an anti-CD20 antibody for treating a neoplastic disease or disorder. Based on the teaching of the references cited by the Examiner, it was not predictable that a combination therapy with an anti-CD40 antibody that enhances the interaction between CD40L and CD40 and an anti-CD20 antibody would have at least additive effect in the treatment of neoplastic diseases characterized by cells expressing CD40, and one skilled in the art would not have had a reasonable expectation of success. Therefore, claims in the present application are not obvious over Siegal et al. in view of Li et al., Hanna et al., Grillo-Lopez, and Benoit et al.

The Examiner further states that the asserted unexpected results based on the Examples in the instant specification do not appear unexpected nor commensurate in scope with the claimed invention. Applicant respectfully disagrees with the Examiner. As discussed above, based on the teachings of the references cited by the Examiner, one skilled in the art would not reasonably expect that a combination with an anti-CD40 antibody that enhances the interaction between CD40L and stimulates CD40 and an anti-CD20 antibody would provide at least additive effects for treating a neoplastic disease or disorder characterized by cells expressing CD40. Thus, the results shown in the Examples in the present application were unexpected.

In addition, Applicant respectfully notes that although the experiments described in the Examples were carried out in animal models, these models were recognized as correlating to a neoplastic disease condition, and one skilled in the art would accept the model as reasonably correlating to the condition. Experimental conditions tested in the Examples of the present application provide an adequate basis for concluding that similar results would be obtained within the scope of the claims.

The Examiner further states that the Experimental model does not compare two doses of either anti-CD40 antibody or anti-CD20 antibody as a control of providing the same amount of therapeutic antibodies in comparison to the combination of anti-CD40 antibody and anti-CD20 antibody. Applicant respectfully notes that using twice the dosage of an antibody may not always

result in higher efficacy if the dosage used is the optimized dosage. As indicated in the Declaration by Dr. Lewis, the 4 mg/kg dosing level (total 9 doses) was considered optimized dosing level for rituximab and dacetuzumab (a humanized antibody of S2C6) in the Ramos lymphoma xenograft model, and thus, one skilled in the art would not consider that any additional benefit that was observed in the combination therapy, as compared to the monotherapy, was contributed by the increase of the total antibody dose in the combination therapy. The data in the Declaration demonstrated that the combined activity of dacetuzumab and rituximab (4 mg/kg each) was significantly greater than that of dacetuzumab and rituximab alone at the 8 mg/kg dosing level (P-value of 0.0041 and 0.0021, respectively); and the median time to reach the 1,000 mm³ tumor volume was 58.7 days for dacetuzumab (8 mg/kg), 34.1 days for rituximab (8 mg/kg), and >100 days for the dacetuzumab plus rituximab combination (4 mg/kg each). The study showed that the *in vivo* activity of the dacetuzumab-rituximab combination appears to be greater than additive, and dacetuzumab is capable of improving the *in vivo* efficacy of rituximab.

In addition, it was surprising for one skilled in the art that the anti-CD40 antibody was capable of improving the *in vivo* efficacy of the anti-CD20 antibody in mice with lymphoma cells that were resistant to the anti-CD20 antibody treatment (RITUXAN® resistant lymphoma cells) as measured by tumor volume and number of tumor free mice. As shown in Fig. 5 in the present application, the anti-CD20 antibody alone (at 4 mg/kg, total 9 doses) had not significantly reduced the rate of tumor volume increase and all mice in this treatment group died or were forced to sacrifice because of the tumor size after 24 days post treatment. The anti-CD40 antibody (at 4 mg/kg, total 9 doses) treatment had reduced the rate of tumor volume, but only 1/10 mice treated was tumor free. In contrast, 10/10 mice treated with both the anti-CD40 antibody and the anti-CD20 antibody (4 mg/kg each, total 9 doses) were tumor free. One skilled in the art would not have expected this effect in mice with tumor cells that were resistant to one of the antibodies used in the combination treatment. In view of the above, the beneficial results achieved by the combination of the anti-CD40 antibody and the anti-CD20 antibody was unexpected.

Accordingly, Applicants respectfully submit that claims 1-8, 14-15, 32-33, 36-39, 46-52, and 55 are not obvious over Siegall et al. in view of Li et al., Hanna et al., Grillo-Lopez, and Benoit et al. Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-18 and 31-53 of copending USSN 11/537,559.

Applicant respectfully requests that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/537,559, at which time Applicant will address this issue. Applicant respectfully notes that claims 1-18 and 31-53 in USSN 11/537,559 have been withdrawn from consideration.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392002400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

Electronic Signature: /Jie Zhou/
Jie Zhou

Registration No.: 52,395
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5922